Mol. Immunol. 28:287-94 (1991) ("Eldridge"), and Jeffery *et al., Pharmaceutical Research* 10:362-68 (1993) ("Jeffery"). Office Action, page 4. The rejection is respectfully traversed.

It appears that the maintenance of this rejection is due, at least in part, to a misunderstanding of Applicants' statements in the previous Amendment (filed January 31, 2001). In particular, Applicants described the invention as follows:

> The invention relates to "microspheres that release . . . antigen and/or adjuvant in three phases: an initial burst, a slow release, and a second burst."[1] An important aspect of the invention is the relative timing of the initial and second burst, as these provide an initial immunization with antigen (i.e., the initial burst), followed, after an appropriate interval, by a booster immunization (i.e., the second burst). *See* Applicants' specification, at 5, lines 30-32. Page 45, lines 43-47, of the specification states that "the microspheres are preferably designed to produce an in vitro second burst at the same time." Thus, the timing between the initial and second burst is the same for the microspheres in a particular population.
>
> Such a population is described in the application at page 6, lines 1-14, which relates to a composition comprising microspheres sharing the described properties. This microsphere population represents one embodiment of the invention originally described in the application. A second embodiment is described in a later passage on page 6, which relates to a composition containing multiple populations of microspheres with different properties. *See* Applicants' specification, at 6, line 18-page 7, line 2. Specifically, this later passage states:
>
> > Another aspect of the invention is a composition for use as a vaccine comprising about one to 100 antigens encapsulated in ***a mixture of about two to 50 PLGA microsphere populations***, wherein
> >
> > * * *

[1] The "initial burst" corresponds to the "first antigen burst phase" recited in Claim 1; the "slow release" corresponds to the "second slow release phase" of Claim 1; and the "second burst" corresponds to the "third antigen burst phase" of Claim 1. Thus, as used in Claim 1, the terms "first," "second," and "third" refer to the first, second and third phases of the triphasic release profile, and the release of antigen during each phase is referred to in Claim 1 as "antigen bursts" in the first and third phases, separated by a "slow release" in the second phase.

> the antigen is released from the microspheres in a triphasic pattern, wherein about 0.5 to 95% of the antigen is released in an initial burst, about 0 to 50% is released over a period of about 1 to 180 days, and the remaining antigen is released in a second burst in ***one microsphere population*** after about 1 to 30 days, in ***a second microsphere population*** after about 30 to 90 days, and in ***additional microsphere populations*** after about 90 to 180 days.

(Emphasis added.) This passage clearly refers to a mixture of microsphere populations wherein each population has a [triphasic] release profile that differs from that of the other populations. Thus, this second embodiment of the invention relates to mixed populations, wherein each population has a characteristic [triphasic] release profile.

Considering the first embodiment described above in conjunction the second embodiment, one of skill would readily appreciate that the first embodiment relates to a composition comprising an "un-mixed" population of microspheres that is homogeneous with respect to release profile. An important aspect of this embodiment is ***a specific triphasic release profile***, which is designed to release antigen in a manner that is advantageous for vaccine delivery, ***is achieved using a single homogeneous population of microspheres***.

The second embodiment is actually a variation of the first embodiment. That is, the second embodiment relates to a composition comprising a mixture of populations, wherein each population is homogeneous with respect to release profile. Each homogeneous population exhibits a specific triphasic release profile, as in the first embodiment. However, the timing of the second burst can be different in each population. In particular, the second burst is described as occurring "after about 1 to 30 days" for one population, "after about 30 to 90 days" for a second population, and "after about 90 to 180 days" for additional populations. One of skill in the art understands that this description relates to a composition in which multiple homogeneous microsphere populations, of the sort described in the first embodiment, can be combined to give a composition that has a release profile with more than three phases.

Applicants had previously amended Claim 1 to recite "individual microspheres" having the triphasic release profile recited in Claim 1 to clarify that Claim 1 is drawn to the first embodiment. In other words, Claim 1 relates to a composition including a homogeneous population

> of microspheres that exhibits a specific triphasic release profile. Applicants wish to emphasize that Claim 1 is an open-ended "comprising" claim and, therefore, reads on any composition including at least one such [homogeneous] population of microspheres, regardless of the presence of other microsphere populations or other components. Thus, Claim 1 encompasses the second embodiment described above.

Amendment dated January 31, 2000, pages 4-5.

> In response to this point, the Examiner stated:
>
> [A]pplicants argue that Elkridge et al. [*sic*], manipulates the phasic burst by mixing different populations of microspheres, however applicant states that mixed populations are within the scope of claim 1. Therefore, Elkridge et al., teaches homogenous populations.

Office Action, page 4. The Examiner then goes on to point out that Eldridge describes studies using un-mixed, as well as mixed, populations of microspheres, concluding that Eldridge "clearly teaches the use of homogenous populations." *Id.*

These statements suggest that Applicants' point in the previous Amendment was not fully appreciated by the Examiner. It is hoped that the following example will help to clarify this point, which represents an important distinction between the claimed invention and Eldridge and the other references of record. Assume that the following homogeneous microsphere populations have the profiles shown in the Table below. That is, assume that an un-mixed population of microspheres

has the indicated percentage of antigen release over the specified days after suspension in a release medium.

Microsphere Population	Release Profile
IA	99% of release occurring over days 1-3; 1% of release occurring over days 4-65.
IB	1% of release occurring over days 1-30, and 99% of release occurring over days 31-65.
IIA	23% of release occurring over days 1-3, 2% of release occurring over days 4-30, and 75% of release occurring over days 31-65.
IIB	23% of release occurring over days 1-3, 2% of release occurring over days 4-60, and 75% of release occurring over days 61-85.

In this example, homogeneous populations IA and IB do not have triphasic release profiles. However, a triphasic release profile can be produced by mixing populations IA and IB. If the two populations were mixed in equal amounts, it might be expected that about 48% of release would occur over days 1-3, about 1-2% of release would occur over days 4-30, and about 48% of release would occur over days 31-65. Although this mixture of microspheres would have a triphasic release profile, it would not meet the terms of the pending claims. Claim 1 recites that "the microspheres in . . . [a] ***homogeneous*** population have an *in vitro* antigen release profile characterized by ***three*** phases." A formulation produced by combining IA and IB has two homogeneous populations, each having an antigen release profile that is characterized by no more than ***two*** phases. In the IA+IB formulation, no homogeneous population of microspheres exhibits triphasic release. Thus, the IA+IB formulation contains no homogeneous population that has satisfies claim 1's requirement for a homogenous population having an antigen release profile characterized by three phases.

Populations IIA and IIB, on the other hand, are homogeneous populations that exhibit triphasic antigen release. These populations differ with respect to the timing of the third antigen burst phase, which occurs beginning at about 31 days for IIA and at about 61 days for IIB. However, both populations have an antigen release profile characterized by the three phases recited in claim 1. Thus, assuming that the other requirements of claim 1 are met, populations IIA and IIB each, individually meet the terms of claim 1.

Claim 1 also encompasses formulations in which a homogeneous population having the recited triphasic release profile is mixed with one or more other microsphere populations, which may or may not exhibit triphasic release. Thus, for example, population IIA could be mixed with population IA to increase the first antigen burst phase. Alternatively, population IIA could be mixed with population IB to increase the third antigen burst phase. Additionally, the invention clearly contemplates mixing populations such as IIA and IIB to, in effect, provide two booster pulses of antigen at about 31 days and 61 days post-initial immunization. Each of these formulations is a "mixed formulation," but each includes at least one homogenous population of microspheres having an antigen release profile that is characterized by three phases. Thus, each of these formulations (i.e., IIA+IA, IIA+IB, and IIA+IIB) is distinct from the formulation produced by mixing IA+IB. In the latter case, triphasic release is ***only*** achieved through mixing homogeneous populations, neither of which exhibits triphasic release. By contrast, in formulations within the scope of claim 1, microsphere populations may be mixed, but the formulation must contain at least one homogeneous population that exhibits triphasic release.

This is an important difference between the claimed composition and those disclosed in Eldridge. The Examiner notes that Eldridge "used homogenous populations wherein the homogenous population was 1-10 um and another homogenous population of 20-125 um diameter microspheres (page 290 and fig. 2)." Office Action, page 4. The Examiner's conclusion that Eldridge "clearly teaches the use of homogenous populations" (*id.*) misses the point that neither of these homogeneous populations exhibits triphasic release. Rather, Fig. 2 in Eldridge indicates that, for each population, antigen release increased to a maximum and then decreased. Eldridge's two "homogeneous" populations are analogous to populations IA and IB in the example given above. The combination of the two Eldridge populations is thus analogous to the IA+IB formulation. As described above, while the individual populations are homogeneous, they do not exhibit triphasic release. Triphasic release can be achieved by mixing the two populations; however, the result is that triphasic release is provided by a mixed population, not by a homogeneous population. Thus, Eldridge fails to teach or suggest a microsphere population that is both homogeneous and releases antigen in three phases, as recited in claim 1.

Because Eldridge fails to teach or suggest a homogeneous population of microspheres that has "an *in vitro* antigen release profile characterized by three phases," Eldridge necessarily fails

to teach or suggest a homogenous population that has the ***specific*** triphasic release profile recited in claim 1, namely:

> a first antigen burst phase, wherein about 0.5 to 30 percent of the antigen is released from the microspheres over a period of about three days after suspension of the microspheres in a release medium; a second slow release phase after the first phase, extending from about the fourth to at least about the thirtieth day after suspension, wherein the daily release of antigen from the microspheres is less than in the first antigen burst phase or a third antigen burst phase; and the third antigen burst phase after the second phase, wherein antigen is released from the microspheres at a rate of greater than 10 percent per week, during a period of from about seven to about 30 days, starting from about 30 to about 180 days after suspension.

Applicants note that Fig. 2 and the passage cited by the Examiner describe the results of measuring the plasma antibody titer in response to a single administration of antigen-containing microspheres. By contrast, Applicants' claims define the antigen release profile in terms of *in vitro* release of antigen after suspension in a release medium. The *in vitro* release profiles for Eldridge's compositions cannot be derived from the data shown in Fig. 2 or the passage relied on by the Examiner. There is simply nothing in Eldridge that would lead one skilled in the art to select the specific triphasic release profile recited in claim 1. Moreover, even if this were not true, Eldridge teaches that a triphasic release profile is obtained by mixing different populations of microspheres, not by producing a homogenous population with the capability.

The Office Action continues: "[A]pplicants argue that triphasic release is not taught by the combination of references." Office Action, page 5. ***Applicants wish to state, in the most emphatic terms possible, that this is <u>not</u> Applicants' argument.*** As discussed in the Examiner Interview, and as reiterated in the last Amendment, ***Applicants argue that the cited references fail to teach or suggest a <u>homogenous</u> microsphere population with the <u>specific triphasic release profile</u> recited in the pending claims.***

The Examiner's discussion of Sanders may or may not establish that Sanders teaches triphasic release. However, this is not the point. The proper focus of the obviousness inquiry is on what is ***claimed***. In considering whether the cited references teach or suggest the invention, it is necessary to determine whether the cited references teach or suggest ***every element recited in the claims***. It is not permissible to distill the invention down to a its "gist"—here, triphasic release—and

then reject the claims over references that arguably disclose the gist, but not the specifics of the invention. Nor is it permissible to disregard any element of the claims.

Yet the Examiner has, in effect, disregarded the specific release profile recited in claim 1 and quoted above. Nothing in the Office Action indicates where ***this release profile*** is found in the cited references. Nor does anything in the Office Action indicate why one skilled in the art would be motivated to modify or combine the teachings of the cited references to achieve ***this release profile***. Moreover, the Office Action cites no reason as to why one skilled in the art would have had a reasonable expectation that a homogeneous population of microspheres having ***the recited release profile*** could be produced. This deficiency is particularly aggegious, given that Applicants' previous Amendment outlined the requirements for establishing a *prima facie* case of obviousness. Thus, the Amendment stated: "The three elements of a prima facie case of obviousness are (1) the reference(s) must teach or suggest all of the elements of the claimed invention, (2) there must some motivation for combining or modifying the teachings of the references to arrive at the claimed invention, and (3) the reference(s) or knowledge in the art must provide a reasonable expectation of success, i.e., a reasonable assurance that the claimed invention would work." Amendment dated January 31, 2001, pages 8-9.

Considering the first element of a *prima facie* case, the references fail to teach or suggest a homogeneous population of microspheres having the specific realease profile recited in claim 1. Nothing in the Office Action even addresses this point. Applicants submit that this omission is due to the fact that none of the cited references even hints at the desirability of the recited release profile. Thus, not only ***has*** the Examiner failed to establish the first element of a *prima facie* case of obviousness, the Examiner ***cannot***, in fact, establish this element based on the references of record. ***If the Examiner maintains this rejection, the Examiner must cite reference(s) that teach or suggest a homogeneous population of microspheres having the specific release profile recited in claim 1. If the Examiner is relying on personal knowledge of this area, Applicants respectfully request an affidavit from the Examiner under M.P.E.P. § 2144.03***, which states:

> When a rejection is based on facts within the personal knowledge of the examiner, the data should be stated as specifically as possible, and the facts must be supported, when called for by the applicant, by an affidavit from the examiner.

Turning to the second element of a *prima facie* case, that of motivation to combine or modify the references, Applicants pointed out in the last Amendment that the Examiner had failed to consider this element and requested such consideration, stating:

> Applicants earnestly request the Examiner to consider ***why*** one skilled in the art would combine these references and modify their teachings to arrive at the specifically claimed invention. The Office Action states that "the combined teachings of the prior art suggest to a person of skill in the art that compositions containing various volumes of antigen can be encapsulated into microspheres for controlled release of antigen." Perhaps . . . ., but the combined teachings of the prior art fail to suggest the ***recited*** antigen release profile. Well-established Federal Circuit precedent makes it clear that obviousness cannot be established merely by showing that the invention would have been possible, in the absence of some specific reason for developing the invention. *See* M.P.E.P. § 2143.01 (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Thus, even assuming *arguendo* that a person of skill in the art could have made microspheres having the recited profile, no *prima facie* case is established if the art fails to suggest a reason for doing so. The record is devoid of any such reason.

Id., pages 11-12. The record is still devoid of any reason why one skilled in the art would have been motivated to make a homogeneous population of microspheres having the recited antigen release profile. Applicants' request for the Examiner to explain how, in the Examiner's view, the cited references satisfy the second requirement for a *prima facie* case has not been addressed in any way. This treatment is directly contrary to Federal Circuit case law, which makes it clear that:

> ***a rejection cannot be predicated on the mere identification . . . of individual components of claimed limitations***. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

In re Kotzab, at 1369-1372 (emphasis added).

If the Examiner maintains this rejection, the Examiner must explain why one skilled in the art would have attempted to produce a homogeneous population of microspheres having the specific release profile recited in claim 1. If the Examiner is relying on personal knowledge of this area, Applicants respectfully request an affidavit from the Examiner under M.P.E.P. § 2144.03.

Finally, in the last Amendment, Applicants pointed out that the previous Office Action was also deficient in failing to establish the third element of a *prima facie* case, namely a reasonable expectation of success. In particular, Applicants stated:

> [T]he record is devoid of any reasonable expectation that [the claimed] . . . population of microspheres could be produced. The rationale for the rejection appears to assume that art was developed to a point that one of skill could produce a homogeneous population of PLGA microspheres having any desired profile. To support this position, the Examiner has cited evidence that a number of the parameters that affect the release characteristics of PLGA polymers were known before the filing date of the invention. But such evidence does not indicate that any desired release profile could be achieved. Nor does this evidence establish that the interactions among the various parameters affecting release were sufficiently well-understood that one skilled in the art would know that a particular combination of parameters would produce a ***homogeneous*** population of microspheres with ***the recited release profile***. Accordingly, the prior art does not provide any reasonable assurance that the claimed population of microspheres could be produced.

Id., page 13. The Office Action fails to address this point in any way, and the record therefore remains devoid of any reasonable expectation that the invention could be made. Thus, the third requirement for a *prima facie* case remains unsatisfied.

If the Examiner maintains this rejection, the Examiner must explain why one skilled in the art would have had a reasonable expectation that a homogeneous population of microspheres having the specific release profile recited in claim could be produced. If the Examiner is relying on personal knowledge of this area, Applicants respectfully request an affidavit from the Examiner under M.P.E.P. § 2144.03.

Not even one element of a *prima facie* case has been established with respect to a homogeneous population of microspheres having the recited release profile. Applicants do not believe it necessary to address the Examiner's specific comments regarding Sanders because these comments are aimed at establishing only that Sanders teaches microspheres capable of triphasic release. Applicants could take issue with this conclusion but choose not to, in the interest of simplifying the issues. Accordingly, Applicants respectfully submit that it does not matter whether Sanders teaches triphasic release or not. What matters is that Sanders neither teaches nor suggests the recited triphasic release profile.

With respect to Jeffery, Applicants stated in the last Amendment:

> Jeffery additionally taught the use of smaller microspheres than recited in Applicants' claims. Applicants have demonstrated that alteration of production parameters of PLGA microspheres leads to dramatically different release characteristics, and Eldridge and Jeffery both showed that particles as small as those used by Jeffery are rapidly phagocytized and degraded so that triphasic release would not be possible from such microspheres.

Id., page 13. In response, the Examiner stated that "Jefferies et al. [*sic*], used smooth sphereical microparticles 1-2um in diameter, however claim 1 does not exclude the use of including [*sic*] these homogenous microspheres because it contains open-ended claim language." Office Action, page 6. Applicants agree with the Examiner's statement, but respectfully point out that it is irrelevant to the obviousness inquiry. Applicants' point was that the small particles described in Jeffery could not have a triphasic release profile. Thus, these particles neither teach nor suggest any triphasic release profile, much less the specific triphasic release profile recited in claim 1. Jeffery, therefore, does not remedy the deficiencies of Sanders and Eldridge discussed above.

As no *prima facie* case of obviousness over Sanders, Eldridge, and Jeffery has been, or can be, established, withdrawal of the § 103 rejection is respectfully requested.

Sanders, Eldridge, Jeffery, and Wang

Claims 5-7 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sanders, in view of Eldridge and Jeffery, and further in view of Wang *et al., J. Controlled Release* 17:23-32 (1991) ("Wang"). This rejection is respectfully traversed.

Wang is cited as teaching the encapsulation of adjuvant in microspheres. The Examiner implicitly accepts Applicants' statement in the last Amendment that "Wang does not provide a teaching or suggestion of a triphasic release profile meeting Applicants' claim limitations," and maintains that the primary references provide this teaching. *See* Amendment dated January 31, 2001, page 14 and Office Action, page 7. Applicants respectfully point out that, in the last Amendment, Applicants stated that:

> like Sanders, Eldridge, and Jeffery, Wang fails to teach or suggest a homogeneous population of microspheres that encapsulate antigen and have the recited release profile, fails to provide any motivation for making such a population, and fails to provide any reasonable assurance that such a population could be made. ***If the Examiner maintains this rejection, the Examiner is respectfully requested to address these points.***

Id. (emphasis added.) As this request was not addressed, it is reiterated. In addition, Applicants respectfully point out that Applicants are not requesting the Examiner to perform some academic exercise. Rather, Applicants are simply requesting the Examiner to do what the law requires to make out a *prima facie* case of obviousness. If, as Applicants believe, the Examiner cannot establish a *prima facie* case, the Examiner must withdraw the § 103 rejection. Such withdrawal is respectfully requested.

Sanders, Eldridge, Jeffery, and Newman

Claims 8 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sanders, in view of Eldridge and Jeffery, and further in view of Newman *et al., AIDS Research and Human Retroviruses* 8:1413-18 (1992) ("Newman"). This rejection is respectfully traversed.

Newman is cited as teaching the adjuvant QS21. The Examiner implicitly agrees that Newman does not teach or suggest the recited triphasic release profile, since the Examiner relies on the primary references for this teaching. As discussed above, the reliance is misplaced, since the primary references fail to meet any of the requirements for a *prima facie* case. Therefore, the § 103 rejection cannot properly be maintained, and its withdrawal is respectfully requested.

Conclusion

In view of the foregoing, Applicants believe that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner does not issue a Notice of Allowance, the law requires that the Examiner:

(1) point out, with specificity, now the cited references teach or suggest ***every single element*** of the claims, and in particular how the references teach or suggest a ***homogeneous*** population of microspheres with ***the recited release profile***;

(2) state ***why*** one skilled in the art would combine these references and modify their teachings to arrive at the specifically claimed invention; and

(3) state how one skilled in the art would know that a particular combination of parameters would produce a ***homogeneous*** population of microspheres with ***the recited release profile***. If the Examiner does not identify how the cited references support these points, as discussed above, ***Applicants respectfully request an affidavit from the Examiner under M.P.E.P. § 2144.03 In addition, if the Examiner does not allow this application, an Examiner interview is respectfully requested.***

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 337-8891.

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APPENDIX A

CLAIMS PENDING IN USSN 08/846933

1. (Five Times Amended) A composition comprising a homogeneous population of polylactide or poly (lactide-co-glycolide) (PLGA) polymer microspheres encapsulating an antigen, wherein said homogeneous population is produced from an emulsion comprising aqueous antigen and a polylactide or PLGA polymer, and

(a) the polymer has a ratio of lactide to glycolide of about 100:0 to 50:50 weight percent;

(b) the polymer has an inherent viscosity of about 0.1 to 1.2 dL/g;

(c) the microspheres in said homogeneous population have a median diameter of about 20 to 100 μm; and

(d) the microspheres in said homogeneous population have an *in vitro* antigen release profile characterized by three phases: a first antigen burst phase, wherein about 0.5 to 30 percent of the antigen is released from the microspheres over a period of about three days after suspension of the microspheres in a release medium; a second slow release phase after the first phase, extending from about the fourth to at least about the thirtieth day after suspension, wherein the daily release of antigen from the microspheres is less than in the first antigen burst phase or a third antigen burst phase; and the third antigen burst phase after the second phase, wherein antigen is released from the microspheres at a rate of greater than 10 percent per week, during a period of from about seven to about 30 days, starting from about 30 to about 180 days after suspension.

4. (Amended) The composition of Claim 1 wherein the median diameter of the microspheres in said homogeneous population is about 30 μm.

5. The composition of Claim 1 further comprising an adjuvant.

6. (Amended) The composition of Claim 5 wherein the adjuvant is encapsulated in microspheres.

7. (Amended) The composition of Claim 5 wherein the adjuvant is coencapsulated with the antigen in the microspheres of said homogenerous population.

8. The composition of Claim 5 wherein the adjuvant is QS21.

9. The composition of Claim 1 further comprising a soluble antigen.

23. (Twice amended) The composition according to Claim 1 wherein the second slow release phase extends over a period of about 30 days.

24. (Twice amended) The composition according to Claim 1 wherein the second slow release phase extends over a period of about 60 days.

25. (Twice amended) The composition according to Claim 1 wherein the second slow release phase extends over a period of about 90 days.

26. (Twice amended) The composition according to Claim 1 wherein the second slow release phase extends over a period of about 120 days.

27. (Twice amended) The composition according to Claim 1 wherein the second slow release phase extends over a period of about 180 days.

28. The composition of Claim 1 wherein the polymer microspheres are polynucleotide(D-L-lactide-co-glycolide) microspheres.